

University of Dundee

Propranolol in the treatment of infantile haemangiomas

Wedgeworth, E; Glover, M; Irvine, A D; Neri, I; Baselga, E; Clayton, T H

Published in:
British Journal of Dermatology

DOI:
[10.1111/bjd.14233](https://doi.org/10.1111/bjd.14233)

Publication date:
2016

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Wedgeworth, E., Glover, M., Irvine, A. D., Neri, I., Baselga, E., Clayton, T. H., Beattie, P. E., Bjerre, J. V., Burrows, N. P., Foelster-Holst, R., Hedelund, L., Hernandez-Martin, A., Audrain, H., Bhate, K., Brown, S. J., Baryschpolec, S., Darne, S., Durack, A., Dvorakova, V., ... Flohr, C. (2016). Propranolol in the treatment of infantile haemangiomas: lessons from the European Propranolol In the Treatment of Complicated Haemangiomas (PITCH) Taskforce survey. *British Journal of Dermatology*, 174(3), 594-601. <https://doi.org/10.1111/bjd.14233>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Propranolol in the treatment of infantile haemangiomas: Lessons from the European Propranolol In the Treatment of Complicated Haemangiomas (PITCH) Taskforce Survey

Wedgeworth E¹, Glover M², Irvine AD³, Neri I⁴, Baselga Torres E⁵, Clayton TH⁶, Beattie P E⁷, Bjerre JV⁸, Burrows NP⁹, Foelster-Holst R¹⁰, Hedelund L¹¹, Hernandez-Martin A¹², Audrain H¹³, Bhate K¹⁴, Brown SJ¹⁵, Baryschpolec S¹⁶, Darne S¹⁷, Durack A⁹, Dvorakova V³, Gach J¹⁸, Goldstraw N¹⁹, Goodyear H²⁰, Grabczyńska S²¹, Greenblatt D¹⁹, Halpern J²², Hearn RMR¹⁵, Hoey S²³, Hughes B¹⁶, Jayaraj R²⁴, Johansson EK²⁵, Lam M¹⁴, Leech S²⁶, O'Regan GM³, Morrison D²⁷, Porter W²⁸, Ramesh R²², Schill T³⁸, Shaw L¹³, Taylor AEM²⁶, Taylor R²⁹, Thomson J¹, Tiffin P³⁰, Tsakok M³¹, Janmohamed SR³², Laguda B³³, McPherson T³¹, Oranje A³⁴, Patrizi A⁴, Ravenscroft J¹⁴, Shahidullah H³⁵, Solomon L², Svensson A³⁶, Wahlgren CF³⁷, Hoeger PH³⁸, Flohr C¹

¹ Department of Paediatric Dermatology, St John's Institute of Dermatology, Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK

² Department of Paediatric Dermatology, Great Ormond Street Hospital NHS Foundation Trust, London, UK

³ Department of Paediatric Dermatology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland

⁴ Dermatology Department of Experimental, Diagnostic and Specialty Medicine (DIMES), S. Orsola-Malpighi Hospital, Bologna University, Italy

⁵ Pediatric Dermatology Unit, Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

⁶ Department of Paediatric Dermatology, Royal Manchester Children's Hospital, Manchester, UK

⁷ Department of Paediatric Dermatology, Royal Hospital for Sick Children, Glasgow, UK

⁸ Department of Paediatrics, University Hospital Aarhus, Denmark

⁹ Department of Dermatology, Addenbrooke's Hospital, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK

¹⁰ Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Germany

¹¹ Department of Dermatology, University Hospital Aarhus, Aarhus, Denmark

¹² Department of Dermatology, Hospital Infantil Niño Jesús, Madrid, Spain

¹³ Department of Paediatric Dermatology, University Hospitals Bristol NHS Foundation Trust, UK

¹⁴ Department of Paediatric Dermatology, Nottingham Children's Hospital, Nottingham, UK

¹⁵ Department of Dermatology, Ninewells Hospital and Medical School, Dundee, UK

¹⁶ Department of Dermatology, Portsmouth Hospital NHS Trust, Portsmouth, UK

¹⁷ Department of Dermatology, South Tees Hospital NHS Foundation Trust, Middlesbrough, UK

¹⁸ Department of Dermatology, University Hospitals Coventry and Warwickshire, Coventry, UK

- ¹⁹ Department of Dermatology, St George's University Hospitals NHS Foundation Trust, London, UK
- ²⁰ Department of Paediatric Dermatology, Heart of England NHS Foundation Trust, Birmingham, UK
- ²¹ Department of Dermatology, Buckinghamshire Healthcare NHS Trust, Amersham, UK
- ²² Department of Dermatology, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
- ²³ Department of Dermatology, Royal Victoria Hospital, Belfast, Northern Ireland, UK
- ²⁴ Department of Paediatrics, South Tees Hospital NHS Foundation Trust, UK
- ²⁵ Dermatological and Venereal Clinic, Södersjukhuset, Stockholm, Sweden
- ²⁶ Department of Paediatric Dermatology, The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK
- ²⁷ Department of Paediatric Ophthalmology, Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK
- ²⁸ Department of Paediatric Dermatology, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK
- ²⁹ Department of Ophthalmology, York Teaching Hospital NHS Foundation Trust, York, UK
- ³⁰ Department of Ophthalmology, City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK
- ³¹ Department of Dermatology, Oxford University Hospitals, Oxford, UK
- ³² Department of Dermatology, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Laarbeeklan 101, 1090 Brussels, Belgium
- ³³ Department of Paediatric Dermatology, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK
- ³⁴ Department of Dermatology (Paediatric Dermatology and Hair), Dermicis, Alkmaar and Foundation/Network for Pediatric Dermatology Rotterdam, Rotterdam, The Netherlands
- ³⁵ Department of Dermatology, Derby NHS Foundation Trust, Derby, UK
- ³⁶ Lund University, Institute of Clinical Research in Malmö, Skåne University Hospital, Department of Dermatology, Malmö, Sweden
- ³⁷ Dermatology Unit, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
- ³⁸ Departments of Paediatrics & Paediatric Dermatology, Catholic Children's Hospital Wilhelmstift, Hamburg, Germany

Corresponding author

Carsten Flohr, Department of Paediatric Dermatology, St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK; Tel: 020 7188 7188, extension 51601; Fax: 020 7188 6334; email: carsten.flohr@kcl.ac.uk

Running head

The European PITCH survey

Funding statement

This study had no specific funding. CF holds a UK National Institute for Health Research (NIHR) Senior Career Development Fellowship (CDF-2014-07-

1 037). The views expressed in this publication are those of the authors and not
2 necessarily those of the NHS, the NIHR or the UK Department of Health. SJ
3 Brown holds a the Wellcome Trust Intermediate Clinical Fellowship
4 (086398/Z/08/Z).

5

6 Conflict of interest disclosure

7 Peter Hoeger participated in the HEMANGIOL study (funded by Pierre Fabre).

8

9 Word, table & figure count

10 Word count: 3,058

11 Table count: 4

12 Figure count: 1

13

1 **What's already known about this topic?**

- 2 • Oral propranolol is widely prescribed as first line treatment for
- 3 complicated infantile haemangiomas.
- 4 • Anecdotally, prescribing practice differs widely, but no international
- 5 survey has been undertaken to date.

6

7 **What does this study add?**

- 8 • This is the first European study of current practice in the use of oral
- 9 propranolol in infantile haemangiomas, based on the largest case
- 10 series of its kind.
- 11 • The PITCH survey confirms the overall efficacy and safety of
- 12 propranolol, with the majority of paediatric dermatologists using
- 13 2mg/kg/day as therapeutic dose.
- 14 • Any future clinical trial should therefore include a 2mg/kg/day treatment
- 15 arm.

1 **Abstract**

2

3 **Background:** Oral propranolol is widely prescribed as first line treatment for
4 infantile haemangiomas (IHs) and anecdotally prescribing practice differs
5 widely between centres.

6 **Objectives:** The Propranolol In the Treatment of Complicated
7 Haemangiomas (PITCH) Taskforce was founded to establish patterns of use
8 of propranolol in IHs.

9 **Methods:** Participating centres entered data on all of their patients who had
10 completed treatment with oral propranolol for IHs, using an online data
11 capture tool.

12 **Results:** The study cohort comprised 1096 children from 39 centres in eight
13 European countries. 76.1% were female and 92.8% had a focal IH, with the
14 remainder showing a segmental, multifocal or indeterminate pattern. The main
15 indications for treatment were periocular location (29.3%), risk of cosmetic
16 disfigurement (21.1%), and ulceration and bleeding (20.6%). 69.2% of
17 patients were titrated up to a maintenance regimen, which consisted of
18 2mg/kg/day (85.8%) in the majority of cases. 91.4% of patients had an
19 excellent or good response to treatment. Rebound growth occurred in 14.1%
20 upon stopping, of which 53.9% were restarted and treatment response was
21 recaptured in 91.6% of cases. While there was no significant difference in the
22 treatment response, comparing a maintenance dose of <2mg/kg/day versus
23 2mg/kg/day versus >2mg/kg/day, the risk of adverse events was significantly
24 higher (OR=1 vs adjusted OR=0.70 (0.33-1.50), p=0.36 vs 2.38 (1.04-5.46),
25 p=0.04, $p_{\text{trend}} < 0.001$).

- 1 **Conclusions:** The PITCH survey summarises the use of oral propranolol
- 2 across 39 European centres, in a variety of IH phases and could be used to
- 3 inform treatment guidelines and the design of an intervention study.

1 **Introduction**

2 Haemangiomas are the commonest benign tumour of infancy, with a postnatal
3 incidence of around 5%.¹ In the latest International Society for the Study of
4 Vascular Anomalies classification, infantile haemangiomas (IHs) are
5 morphologically subdivided into focal or localised, segmental, indeterminate
6 and multifocal IHs.² They typically develop during the first month after birth
7 and follow a characteristic evolution from early rapid proliferation to a
8 stabilisation and a slow involution phase, which often takes years. Around
9 20% of IHs need medical attention due to complications, for instance
10 bleeding, ulceration or threat to vision.³ Since the serendipitous discovery of
11 the benefit of propranolol in IHs in 2008⁴, it has been rapidly adopted as a first
12 line treatment for complicated lesions, replacing oral corticosteroids. In
13 addition to numerous case series and case reports, three randomised
14 controlled trials have investigated the efficacy of propranolol in IHs, with the
15 largest trial (n=456) comparing a dose of 3mg/kg/day with 1mg/kg/day dose
16 and placebo, which found that the higher dose was significantly superior with
17 regard to treatment efficacy.^{5,6,7} However, this study only used propranolol for
18 a maximum of 24 weeks, excluded patients outside the proliferation phase as
19 well as children with life- or function-threatening or severely ulcerated IHs for
20 ethical reasons, owing to the inclusion of a placebo group.⁵ This would, for
21 instance, have excluded segmental IH (SIHs). 2mg/kg/day is the most
22 commonly reported dose in the literature and between-centre heterogeneity in
23 the use of oral propranolol in complicated IHs is likely, although no survey of
24 clinical practice has so far been conducted across the European paediatric
25 dermatology community to confirm this impression.^{8,9}

1 We therefore founded the Propranolol In the Treatment of Complicated
2 Haemangiomas (PITCH) Taskforce in 2013 with three main objectives: i) to
3 ascertain patterns of propranolol prescribing in Europe, ii) to collect data on
4 the safety and efficacy of oral propranolol, and iii) to help inform the
5 formulation of treatment guidelines as well as the design of future intervention
6 studies.

7

Patients and Methods

Study data on patients who had treatment of an IH with oral propranolol were collected across eight European countries (Denmark, Germany, Ireland, Italy, the Netherlands, Spain, Sweden, and the UK), using the REDCap (Research Electronic Data Capture) electronic database tool (Vanderbilt University, Nashville, Tennessee, USA).¹⁰ The study was conceived and coordinated by the Paediatric Dermatology Department at St John's Institute of Dermatology, Guy's and St Thomas' Hospital NHS Foundation Trust, London, UK, and approved by the Research and Development Department at Guy's and St Thomas' Hospital NHS Foundation Trust.

Data were collected between June 2013 and November 2014. In the UK, invitations to participate were disseminated through the British Society for Paediatric Dermatology (BSPD) membership list. Paediatric Dermatology centres from seven other European countries were also invited to take part. Centres were asked to only enter patients who had completed propranolol therapy for an IH. The following data were collected: country of practice, speciality, patient sex, subtype of IH (focal, segmental or other type, including multifocal IHs), treatment indication (periocular with threat to vision, nasal tip, causing functional disturbance, ulceration, recurrent bleeding, uncomplicated IH on the face other than periocular or nasal tip, parental request, and other indication), age at treatment commencement, adjunctive therapies, pre-initiation screening investigations, treatment dosage and duration, adverse events, treatment response (from 'excellent/complete response', 'good', 'poor' to 'none'), rebound growth, and re-treatment with propranolol.

1 Where individual patient data was incompletely entered, we contacted the
2 study centres to collect missing information.

3 We present primarily descriptive analyses. Age at treatment commencement,
4 duration of treatment, and the age therapy was stopped are presented as
5 medians and ranges due to the non-normal distribution of the data. Odds
6 ratios and corresponding 95% confidence intervals were calculated in relation
7 to treatment response and risk of rebound growth. Following univariate
8 analysis, significant risk estimates were mutually adjusted in logistic
9 regression. The following variables were evaluated as potential confounders:
10 gender, the age treatment was started, the length of treatment, the age
11 treatment was stopped, and the type of IH. The statistical analyses were
12 conducted by CF and EW, using SPSS software (Sun Microsystems Inc.)
13 version 19.0. We followed the STROBE guidelines for the reporting of
14 observational studies throughout.

Results

Data from 1096 patients were entered from 39 individual centres in 8 European countries (Denmark (n=35 patients), Germany (193), Ireland (136), Italy (65), the Netherlands (23), Spain (92), Sweden (72), UK (481)).

Patient demographics and clinical features

The majority (92.8%; 1018) of patients had focal IHs and were female (76.1%). The median age at initiation of propranolol was 17 weeks (range 0.5-396). 19.8% (217) of the total cohort were premature (defined as born at <37 weeks of gestation). 5.5% (60) had a SIH, 0.8% (9) multifocal IHs. Local investigators also entered data on 10 children treated with propranolol for a congenital haemangioma, but these cases were not included in the efficacy-related analyses as they are distinctly different from IHs. Of the focal IHs, 77.2% (786) were treatment initiated in the rapid growth phase, 21.5% (219) during stabilisation and 1.3% (13) in the involution phase. The three main indications for treatment were 'periocular location with threat to vision' (29.3%; 321), 'risk of cosmetic disfigurement on the face' (21.1%; 232) and 'ulceration and bleeding' (20.6%; 226). The other indications are displayed in Fig. 1. At the time of initiation, 87.0% (954) were on no adjunctive treatment, while 6.1% (67) were taking oral glucocorticoids, 2.3% (25) were also undergoing laser therapy, 2.0% (22) were on topical glucocorticoids, and 2.6% (29) were on 'other' therapies, including topical timolol.

Pre-initiation screening

1 69.1% (757) of patients had blood tests before starting propranolol, of whom
2 93.5% (708) had a glucose level, 88.8% (672) a full blood count, 86.0% (651)
3 a renal profile, 82.0% (621) liver function tests, and 61.8% (468) a thyroid
4 profile. 92.3% (1013) underwent a cardiological or radiological investigation
5 before starting propranolol. 88.5% (971) underwent an electrocardiogram
6 (ECG), 67.5% (741) had an echocardiogram (ECHO), 7.7% (84) magnetic
7 resonance imaging (MRI), and 15.7% (172) an abdominal ultrasound. 98.4%
8 of patients underwent a full clinical examination, before treatment was started.
9 54.9% (602) had a specialist cardiology evaluation, and 50.4% (553) were
10 also assessed by a general paediatrician.

11

12 ***Treatment initiation and dosage regimens***

13 89.8% (985) of patients had propranolol initiated in a hospital setting; 44.2%
14 (435) as day cases, 26.4% (260) had an overnight stay, and 29.4% (290) had
15 a hospital stay of two or more nights. The most common investigations
16 undertaken during initiation were heart rate (98.3%, 968) and blood pressure
17 monitoring (98.9%, 974), with 54.0% (532) also having glucose and 32.6%
18 (321) ECG monitoring. 69.2% (759) of patients were started on a lower
19 dosage and subsequently had dose incrementation to a maintenance
20 regimen. The most frequent initiation dosage was 1mg/kg (47.1%, 517).
21 18.6% (204) of patients were started at <1mg/kg/day and 26.2% (288) at
22 2mg/kg/day. The majority of patients had a daily maintenance dose of
23 2mg/kg/day (85.8%, 939). Only 4.8% (52) of the cohort had a daily
24 maintenance dosage of <2mg/kg. 11.0% (103) had a dosage of >2mg/kg.
25 Most children were started on treatment during the rapid growth phase

(71.6%, 785), but in a significant number treatment was initiated in the stabilisation (20.0%, 219) and a few even during the involution phase because of ulceration (1.2%, 13).

Treatment response and rebound growth

The median length of treatment was 32 weeks (range 2-184). 19.8% (215) of patients were reported to have an excellent response compared to 72.0% (782) with a good and 7.0% (76) with a poor or no response seen in 1.2% (13). There was a trend for a higher 'good or excellent' (vs 'poor or no') treatment response in the 2mg/kg/day (adj OR=1.25, 0.43-3.62, p=0.68) and the above 2mg/kg/day dose groups (adj OR=1.74, 0.45-6.57, p=0.42) but the results were statistically not significant, and there was no association with duration of treatment.

With regard to the phase of the IH when treatment was initiated, our results suggest that there is still benefit from treating patients in the stabilisation phase, although the response rate was lower than in the rapid growth phase, with 18.3% of patients having a poor or no response compared to 5.6% of patients in the rapid growth phase.

Most patients (76.8%, 842) had their dose of propranolol titrated down before stopping. The median age at stopping was 56 weeks (range 4-412).

14.1% (154) of patients were reported to experience rebound growth of the IH after stopping treatment. Of those experiencing rebound growth, 53.9% (83) were restarted on propranolol, representing 7.6% of the total cohort. On retreatment, response was recaptured in the vast majority (91.6%).

Predictors of rebound growth

Although the median age when treatment was stopped was lower (52 weeks, interquartile range (IQR) 40-64) in the rebound growth group compared to 56 weeks (IQR 42-72) in the non-rebound growth group, this difference was not statistically significant ($p=0.08$, Table 1). The rebound growth risk reduction was most noticeable in the children who were 70 weeks or older when treatment was stopped ($OR=0.58$, 95% CI 0.34-0.99, $p=0.048$), compared to children in the other age quartiles: up to 40 weeks ($OR=1$, reference group), 40-54 weeks ($OR=0.83$, 0.50-1.37, $p=0.46$), and 54-70 weeks ($OR=0.90$, 0.55-1.48, $p=0.68$; $p_{trend}<0.001$). However, the results became non-significant for children aged 70 weeks and above, when age at treatment initiation and treatment length were taken into account in multivariate logistic regression analysis. The results also did not appreciably change when the analyses were restricted only to children with focal IH or IHs in the rapid growth phase.

Segmental infantile haemangiomas

Our cohort included 60 SIHs. 35.0% (21) had an associated abnormality with cerebral artery malformations, consistent with a diagnosis of PHACE syndrome, being the commonest (15.0%, 9). Other associations are shown in Table 2. The median length of treatment for SIHs was 45 weeks (range 8-139). 31.7% (19) patients showed rebound growth, compared to 13.1% for focal IHs (adjusted $OR=3.33$, 1.85-6.01, $p<0.001$). 16.7% (10) of patients were restarted on propranolol, and all of these recaptured their original treatment response.

Adverse events

19.6% (215) of the cohort experienced an adverse event, and these are shown in Table 1. Of those experiencing side effects, 55.3% (119) continued with propranolol with the dose unchanged. 25.1% (54) had a dose adjustment, and treatment was stopped in 19.5% (42) of cases who experienced side effects, which represented 3.8% of the PITCH cohort. The reasons for treatment cessation were: wheezing (15), sleep disturbance (8), diarrhoea (5), significant hypoglycaemia (4), worsening of the ulceration (4), persistent cough (2), irritability and poor feeding (1), concern about delayed development (1), and one episode of cyanosis.

The risk of experiencing an adverse event was more than twice as high in children on a maintenance dose of over 2mg/kg/day compared to children on a lower treatment dose: adj OR $<2\text{mg/kg/day} = 1$, adj OR $2\text{mg/kg/day} = 0.70$ (0.33-1.50), $p=0.36$ vs adj OR $>2\text{mg/kg/day} = 2.38$ (1.04-5.46), $p=0.04$ ($p_{\text{trend}} < 0.001$), although no individual category of adverse events made a significant standalone contribution to this risk increase. In addition, there was a more than 50% lower rate of adverse events in the children who had their dose incremented compared to those who were started directly on the therapeutic dose (adj OR = 0.48 (0.35-0.65), $p < 0.001$).

Adverse events among children without baseline investigations

The necessity and depth of pre-initiation screening is an area of uncertainty, and we therefore examined the adverse events and resultant changes in propranolol dosages during treatment in patients with pre-initiation screening and those without. The relative adverse events in the groups with/without

1 ECGs and ECHOs prior to commencement were non-significant and are
2 summarised in Table 4. Similarly, there was no significant difference in the
3 frequency of other, non-cardiovascular side effects, such as hypoglycaemia,
4 cold peripheries, sleep disturbance, diarrhoea, and wheezing.
5

1 **Discussion**

2 The PITCH survey confirms the efficacy and safety of propranolol therapy in
3 IHs, with a good or excellent response seen in over 90% of patients. Although
4 there was a trend towards higher efficacy across the dose ranges, the
5 difference between the proportion of good/excellent responses in the
6 2mg/kg/day and the above 2mg/kg/day dose groups was statistically not
7 significant, whereas the risk of adverse events was significantly higher.

8 The PITCH Taskforce survey is the first international survey of its kind,
9 collecting data from eight European countries and to the best of our
10 knowledge represents the largest single case series of children with
11 complicated IHs treated with oral propranolol, although a previous systematic
12 review collected data from 1,264 patients included in 41 individual studies.¹¹

13 Limitations of our survey include the retrospective nature of data collection,
14 which has an inherent risk of reporting bias. Although we strongly encouraged
15 individual study centres to enter all their patients who completed oral
16 propranolol for a IH, there might have been patients with incomplete clinical
17 records and that study centres therefore decided not to enter these patients
18 into the study. It is also possible that the threshold of oral propranolol
19 treatment for IHs changed over the years, as our experience and the
20 published evidence of its efficacy increased. This would have biased the early
21 cases towards greater severity.

22 In addition, the classification of IHs is not straightforward, and this might have
23 resulted in misclassification of some segmental and indeterminate IHs in
24 particular. We also had no information on depth and size of the IH and side
25 effects were reported by physicians, not parents, which could have led to

1 reporting bias. We were also not able to use more objective outcome
2 measures, and there are no long-term follow up data available on this cohort.
3 Another limitation of our survey is that we only included patients who were
4 treated with propranolol. We are therefore not able to say how many patients
5 were not started on oral propranolol because of abnormal baseline
6 investigations. However, the rate of side effects in those who had no baseline
7 investigations was comparable to those who had tests done prior to starting
8 oral propranolol.

9 The strongest evidence for the efficacy of oral propranolol in IH so far comes
10 from a recently published randomised controlled trial that compared a dose of
11 1mg/kg/day with 3mg/kg/day, showing clear superiority of the higher dose in
12 treatment efficacy.² However, we found no difference between 3mg/kg/day
13 and the much more commonly used dose of 2mg/kg/day. Our results also
14 suggest that IHs can benefit from oral propranolol treatment even during the
15 stabilisation phase, in line with other, smaller studies.^{12,13} Furthermore,
16 ulcerated lesions are often refractory to a number of older treatment
17 modalities¹⁴ but may often respond well to propranolol, with 91.6% of IHs
18 treated for ulceration/bleeding having a 'good or excellent' response. This
19 high response rate is in keeping with other published evidence.¹⁵

20 As for potential side effects, the PITCH survey suggests that treatment with
21 propranolol is safe. Most reported side effects were mild with the most
22 common side effects being sleep disturbance and cold peripheries,
23 accounting for 54% of all adverse events. 3.8% of our cohort ceased
24 treatment due to side effects. Hypoglycaemia was reported in only 0.7%,
25 presumably because parents are advised to withhold propranolol at times of

1 reduced oral intake.^{16,17} Whilst adverse events were generally mild, little is
2 known about potential longer term side effects. Propranolol is well known to
3 cross the blood brain barrier and concerns have been raised over the drug's
4 potential to lead to neurodevelopmental delay, and further research and long-
5 term follow up is required.¹⁸

6 In our cohort, there was a clear association between the frequency of adverse
7 events and the treatment dose with twice the number of adverse events seen
8 in the 3mg/kg/day group compared to those receiving 2mg/kg/day or lower
9 doses. Given the lack of significant difference in efficacy between these two
10 doses, it seems prudent to use the lower dose, as long as the observed
11 treatment effect is adequate. In addition, there was a more than 50% lower
12 rate of adverse events in the children who had their dose incremented
13 compared to those who were started directly on the therapeutic dose (adj OR
14 = 0.48 (0.35-0.65), $p < 0.001$), and dose up titration has indeed been
15 recommended in current treatment guidelines.¹⁸

16 The need for in-depth investigations prior to commencement of propranolol
17 remains another area of debate, and our data support a rationalisation of pre-
18 treatment screening, in keeping with a recent European expert consensus
19 statement.¹⁹ While initial recommendations suggested the need for full
20 cardiological investigations with ECGs and ECHOs,²⁰ current US and
21 European consensus guidelines state that full clinical examination and an
22 ECG are sufficient.^{18,21} Since we did not find a significant difference between
23 rates of adverse events in those patients with pretreatment ECHOs and ECGs
24 versus those that started without, apart from a slightly higher rate of
25 bradycardia in those patients who did not undergo a pretreatment ECG (1.6%

1 vs 0.4% $p=0.09$), we feel the additional value of an ECG, in the face of an
2 unremarkable history and physical examination including auscultation,
3 remains uncertain.²²

4 With 60 cases, the PITCH survey assembled the to largest case series of
5 SIHs to date, 15% of whom had underlying cerebral vascular anomalies.

6 There were similar rates of adverse events in this group, when compared to
7 the general cohort. 18.3% of patients with SIHs experienced side effects, but
8 in only 1.7% of cases did this lead to cessation of treatment. No
9 cerebrovascular events were reported, and the efficacy and safety in this
10 group were overall comparable to the rest of the cohort, although the risk of
11 rebound growth was double that of the rest of the cohort, potentially due to the
12 increased depth of these lesions.

13 Rebound growth was seen in 14.1% of the PITCH cohort. Those who were 17
14 months or older when treatment was stopped had a significantly lower risk of
15 rebound growth in univariate analysis, but this effect was lost in multivariate
16 regression analysis. Interestingly, when we stratified rebound growth rates by
17 daily dosage, we found higher rates of rebound growth in the group treated
18 with 3mg/kg/day (27.5% vs 13.0% at 2mg/kg and 16.0% at <2mg/kg). Our
19 results may be explained by the type or size of IHs which necessitated a
20 higher treatment dose. As for rebound growth rates, other studies found these
21 to be between 5% and over 25%.^{3,23,24,25,26,27} Previous predictors of rebound
22 growth after cessation of propranolol have included size and depth of IHs,
23 | SIHs²⁷ were all variables we were not able to examine in this cohort.²⁸

24

1 In summary, oral propranolol has emerged as the first line treatment for
2 complicated IHs. Our large cohort study confirms that it can be used
3 effectively and safely across a range of indications and phases of IH growth.
4 Rebound growth is a significant risk, particularly in SIHs. However, we did not
5 find that using propranolol at 3mg/kg/day reduced this risk significantly. As we
6 found good efficacy across a range of dosages (1-3mg/kg) with no significant
7 difference in efficacy between 2mg/kg/day and 3mg/kg/day, the optimum
8 treatment dose remains under discussion, also because the rate of side
9 effects appeared higher in children treated with 3mg/kg/day. An adequately
10 powered randomised controlled trial comparing 2mg/kg/day with 3mg/kg/day
11 is therefore required.

1 **Contributions:**

2 The PITCH Taskforce was initiated and led by Carsten Flohr. Emma
3 Wedgeworth acted as Co-Principal Investigator. *PITCH Taskforce Steering*
4 *Committee:* Carsten Flohr (Chair), Mary Glover, Alan Irvine, Hussain
5 Shahidullah, and Emma Wedgeworth. *PITCH Study Writing Group:* Eulalia
6 Baselga Torres, Paula Beattie, Jesper Bjerre, Nigel Burrows, Tim Clayton,
7 Carsten Flohr, Regina Foelster-Holst, Mary Glover, Angela Hernandez-Martin,
8 Peter Hoeger, Iria Neri, Alan Irvine, Bisola Laguda, Tess McPherson, Arnold
9 Oranje, Annalisa Patrizi, Jane Ravenscroft, Hussain Shahidullah, Ake
10 Svensson, Carl-Fredrik Wahlgren, and Emma Wedgeworth. All authors were
11 involved in the data collection. Carsten Flohr and Emma Wedgeworth wrote
12 the manuscript, and all other co-authors critically revised the manuscript
13 drafts.

14

1 **Figure 1.** Indications for treatment with oral propranolol

1 **Table 1.** Predictors of rebound growth

2

	Rebound growth	No rebound growth	
Characteristic	Median weeks (IQR) N=154	Median weeks (IQR) N=942	P value
Age at treatment initiation	16 (9-28)	17 (12-28)	0.45
Age when treatment stopped	52 (40-64)	56 (42-72)	0.08
Length of treatment	32 (24-48)	32 (24-48)	0.12

3

4 IQR – interquartile range

- 1 **Table 2.** Structural abnormalities associated with segmental infantile
- 2 haemangiomas

Structural abnormalities associated with segmental infantile haemangiomas	% (n) of segmental infantile haemangiomas (total n=60)
Cerebral artery anomalies	15.0% (9)
Posterior fossa abnormalities	6.7% (4)
Ventricular septal defect	5.0% (3)
Patent foramen ovale	5.0% (3)
Atrial septal defect	5.0% (3)
Sternal cleft/supraumbilical raphe	5.0% (3)
Coarctation of the aorta	3.3% (2)
Patent ductus arteriosus	1.7% (1)
Intracranial haemangioma	1.7% (1)

- 3
- 4

1

2 **Table 3:** Adverse events experienced whilst on oral propranolol treatment

Adverse event	% of total cohort (n)
Sleep disturbance	8.2% (90)
Cold peripheries	4.6% (51)
Wheezing	2.8% (31)
Diarrhoea	1.9% (21)
Symptomatic hypotension	1.6% (18)
Symptomatic hypoglycaemia	0.7% (8)
Symptomatic bradycardia	0.5% (6)
Other	3.3% (36)

3

4

Table 4. Adverse event frequency and resulting dose adjustments in those with/without pre-initiation ECGs and ECHOs

	ECHO Yes	ECHO No	p	ECG Yes	ECG No	p
Total numbers (%)	741 (67.5)	356 (32.5)	-	971 (88.5)	126 (11.5)	-
Adverse events (total)	20.0% (148)	18.9% (67)	0.67	19.2%(186)	23.0%(29)	0.28
Hypotension	1.8% (13)	1.4% (5)	0.67	1.5% (15)	2.4% (3)	0.48
Bradycardia	0.5% (4)	0.6% (2)	0.96	0.4% (4)	1.6% (2)	0.09

3

ECG – electrocardiogram, ECHO - echocardiogram

-
- ¹ Munden A, Butschek R, Tom WL, et al. Prospective study of infantile haemangiomas: incidence, clinical characteristics and association with placental anomalies. *Br J Dermatol* 2014;170:907-13.
- ² Dasgupta R, Fishman SJ. ISSVA classification. *Seminars in Pediatric Surgery* 2014;23:158-61.
- ³ Hemangioma Investigator Group. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. *J Pediatr* 2007;150:291-4.
- ⁴ Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008;358:2649-51.
- ⁵ Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J *et al.* , A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med* 2015;372:735-746.
- ⁶ Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. *Pediatrics* 2011;128:e259-66.
- ⁷ Léauté-Labrèze C, Dumas de la Roque E, Nacka F, et al. Double-blind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants <4 months of age. *Br J Dermatol* 2013;169:181-3.
- ⁸ Marqueling AL¹, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. *Pediatr Dermatol* 2013;30:182-91.

-
- ⁹ Izadpanah A, Izadpanah A, Kanevsky J, Belzile E, Schwarz K. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. *Plast Reconstr Surg* 2013;131:601-13.
- ¹⁰ Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-81.
- ¹¹ Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. *Pediatr Dermatol* 2013; 30: 182-91.
- ¹² Zvulunov A , McCuaig, C, Frieden IJ et al. Oral propranolol therapy for infantile hemangiomas beyond the proliferation phase: a multicenter retrospective study. *Pediatric Dermatology* 2011;28:94–8.
- ¹³ Vivas-Colmenares GV, Bernabeu-Wittel J, Alonso-Arroyo V, Matute de Cardenas JA, Fernandez-Pineda I. Effectiveness of propranolol in the treatment of infantile hemangioma beyond the proliferation phase. *Pediatric Dermatology* 2015; 32: 348-52.
- ¹⁴ Kim HJ, Colombo M, Freiden IJ. Ulcerated haemangiomas: clinical characteristics and response to therapy. *J Am Acad Dermatol* 2001;44:962-72.
- ¹⁵ Caussé S, Aubert H, Saint-Jean M, et al. Propranolol-resistant infantile haemangiomas. *Br J Dermatol* 2013;169:125-9.
- ¹⁶ Martin K, Bleib F, Chamlin SL, Propranolol treatment of infantile hemangiomas: anticipatory guidance for parents and caretakers. *Pediatric Dermatology* 2013;30:155–9.

-
- ¹⁷ Do we have to check glucose in patients with haemangioma of infancy treated with beta-blockers? Janmohamed SR, de Laat PC, Madern GC, Oranje AP. *J Eur Acad Dermatol Venereol* 2011;25:1490.
- ¹⁸ Langley A and Pope E. Propranolol and central nervous system function: potential implications for paediatric patients with infantile haemangiomas. *Brit J Dermatol* 2015;172:13-23.
- ¹⁹ Hoeger PH, Harper JI, Baselga E et al. Treatment of infantile haemangiomas: recommendations of a European expert group. *Eur J Pediatr* 2015; 174: 855-65.
- ²⁰ Manunza F, Syed S, Laguda B et al. Propranolol for complicated infantile haemangiomas: a case series of 30 infants . *Brit J Dermatol* 2010;162:452–8.
- ²¹ Drolet BA, Frommelt PC, Chamlin SL et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics* 2013;131:128-40.
- ²² Raphael MF, Breugem CC, Vlasveld FAE. Is cardiovascular evaluation necessary prior to and during beta-blocker therapy for infantile hemangiomas? A cohort study. *J Am Acad Dermatol* 2015;72:465-72.
- ²³ Giachetti A, Garcia-Monaco R, Sojo M. Long-term treatment with oral propranolol reduces relapses of infantile haemangiomas. *Ped Derm* 2014;31: 14-20.
- ²⁴ Solman L, Murabit A, Gnarra M et al. Propranolol for infantile haemangiomas: single centre experience of 250 cases and proposed therapeutic protocol. *Arch Dis Child* 2014;99:1132–6.

-
- ²⁵ Phillips R J Penington A J , Bekhor PS et al. Use of propranolol for treatment of infantile haemangiomas in an outpatient setting . J Paed Child Health 2012;48:902–6.
- ²⁶ Hermans DJJ, Bauland CG, Zweegers J, Propranolol in a case series of 174 patients with complicated infantile haemangioma: indications, safety and future directions .Brit J Dermatol 2013;168:837–43.
- ²⁷ Ahogo CK, Ezzedine K, Prey S. Factors associated with the relapse of infantile haemangiomas in children treated with oral propranolol. Brit J Dermatol 2013;169:1252–6.
- ²⁸ Balma-Mena A, Chakkittakandiyil A, Weinstein M et al. Propranolol in the management of infantile hemangiomas: clinical response and predictors. J Cut Med Surg 2012;16:169–73.